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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/976,566	11/24/97	POTTER A	9001-0016.01

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EXAMINER	
GRASER, J	
ART UNIT	PAPER NUMBER
1641	11

DATE MAILED: 08/06/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/976,566	Applicant(s) Potter et al.
	Examiner Graser, Jennifer	Group Art Unit 1641

☒ Responsive to communication(s) filed on *Amdt. C with Declaration 5/24/99*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *37-45* is/are pending in the application.

Of the above, claim(s) *38, 39, 42, and 43* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *37, 40, 41, 44, and 45* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

1. Acknowledgment and entry of the Amendment submitted 5/24/99, Paper No. 10C is made. Claims 37, 40, 41, 44 and 45 are currently under examination.

Claim Rejections - 35 USC § 112

2. Claim 37, 40, 41, 44 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 37 is vague and indefinite because of the term "capable of". The capability is not the same thing as actually performing the function. A positive recitation of the function is required.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 37, 40, 41, 44 and 45 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 6, and 9 of U.S. Patent No. 5,422,110. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of US Patent No. 5,422,110 recite an "immunological carrier system"; however, said carrier system comprises a leukotoxin fused to a selected antigen which reads on the chimeric proteins of the present invention. Claim 5 of US Patent 5,422,110 specifically recites leukotoxin polypeptide fused to GnRH. Although the claims are not identically worded it would have been obvious that the chimeric proteins of the present application could be considered immunological carrier systems.

5. Claims 37, 40, 41, 44 and 45 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No.5,837,268. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of US Patent No.5,837,268 recite a chimeric protein comprising a leukotoxin polypeptide fused to GnRH. Although US Patent 5,837,268 recites the fusing the leukotoxin polypeptide to specific multimers it still reads on the chimeric proteins of the present invention.

6. Claims 37, 40, 41, 44 and 45 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 and 19-22 of U.S. Patent No.5,723,129.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of US Patent No.5,723,129 recite chimeric proteins comprising a leukotoxin polypeptide fused to GnRH. Although US Patent 5,723,129 recites the fusing the leukotoxin polypeptide to specific multimers having more than one GnRH polypeptide, the word "comprising" in the instant claims allow for more than one GnRH as well.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 37, 44 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Potter (5,476,657).

Potter discloses proteins and subunit antigens from *P.haemolytica* for use in stimulating immunity against respiratory diseases such as pneumonia, including shipping fever pneumoniae (see abstract). Vaccines comprising an immunogenic amino acid sequence of *P.haemolytica* leukotoxin, or an amino acid sequence substantially homologous and functionally equivalent thereto, and a pharmaceutically acceptable carrier are disclosed (column 3, lines 3-24). Potter discloses production of recombinant *P.haemolytica* leukotoxin and specifically recites the production of leukotoxin 352 or "LKT 352" (column 17, lines 54-58). It is disclosed that vaccination with LKT 352 in combination with a *P.haemolytica* saline extract significantly

reduced bovine respiratory disease morbidity and bovine respiratory disease mortality as compared to treatment with a placebo (column 25, lines 43-48). It is also specifically disclosed that prior to immunization, it may be desirable to increase the immunogenicity of the particular Pasteurella protein, or an analog of the protein, by linking the antigenic peptide to a carrier (column 13, lines 10-15). It is disclosed that suitable carriers may be proteins, polysaccharides, VP6 polypeptides of rotaviruses, viral proteins (column 13, lines 9-50).

9. Claim 37, 44 and 45 is rejected under 35 U.S.C. 102(e) as being anticipated by Potter (5,238,823).

Potter is entitled to a filing date more than one year prior to the effective filing date of the present case.

Potter et al. disclose the expression of a fusion protein comprising leukotoxin having substantially the sequence of leukotoxin fused to IL-2 (a selected antigen) for use as a vaccine against shipping fever pneumoniae (see Fig. 2 for the plasmid encoding the fusion protein, example 2 for the expression of the protein as well as example 4 for the method of administration of the vaccine in a carrier to calves).

Response to Applicant's Arguments regarding Potter 5,476,657 and Potter 5,238,823:

10. Applicants argue that the present invention utilizes leukotoxin as a carrier, not as an antigen for which specific immunity is targeted. The argue that Potter 5,476,657 is using VP6 as a carrier protein and not the antigen of interest. These arguments have been fully and carefully considered but are not deemed persuasive. Potter disclose that proteins, polysaccharides, VP6

polypeptides of rotaviruses, viral proteins (column 13, lines 9-50) may be linked to the leukotoxin. These compositions would be structurally identical to those instantly claimed, i.e., a chimeric protein comprising leukotoxin coupled to an antigen.

Applicants also argue that Potter 5,238,823 disclose leukotoxin fused to IL2; however the claims specifically exclude cytokines. This has been carefully considered but is not deemed persuasive. Applicants arguments are not commensurate in scope with the claimed invention. The instant claims, as currently written, read on any antigen and do not exclude cytokines. Applicants should amend the claims to exclude cytokines.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

12. Claims 37, 40, 41 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over as being unpatentable over Potter (5,476,657) in view of Bell et al (5,114,711).

Potter discloses proteins and subunit antigens from *P.haemolytica* for use in stimulating immunity against respiratory diseases such as pneumonia, including shipping fever pneumoniae (see abstract). Vaccines comprising an immunogenic amino acid sequence of *P.haemolytica* leukotoxin, or an amino acid sequence substantially homologous and functionally equivalent thereto, and a pharmaceutically acceptable carrier are disclosed (column 3, lines 3-24). Potter discloses production of recombinant *P.haemolytica* leukotoxin and specifically recites the production of leukotoxin 352 or "LKT 352" (column 17, lines 54-58). It is disclosed that vaccination with LKT 352 in combination with a *P.haemolytica* saline extract significantly reduced bovine respiratory disease morbidity and bovine respiratory disease mortality as compared to treatment with a placebo (column 25, lines 43-48). It is also specifically disclosed that prior to immunization, it may be desirable to increase the immunogenicity of the particular Pasteurella protein, or an analog of the protein, by linking the antigenic peptide to a carrier (column 13, lines 10-15). It is disclosed that suitable carriers may be proteins, polysaccharides, VP6 polypeptides of rotaviruses, viral proteins (column 13, lines 9-50). However, Potter does not particularly exemplify chimeric proteins comprising a leukotoxin derived from *P.haemolytica* and gamma-interferon or active fragment thereof.

Bell et al. disclose the recombinant production of chimeric proteins which are composed of two covalently linked cell modulators in a linear polypeptide sequence. It is taught that the cell modulators are interferons, lymphokines or cytokines (abstract). The '711 Bell et al patent specifically claims compositions comprising gamma IFN-lymphotoxin and teaches these compositions admixed with a carrier. Bell et al '711 discloses that immune interferon (IFN-gamma) has antiproliferative and immunomodulating activity (column 1, lines 38-43).

At the time the invention was made it was well known in the art to those of ordinary skill that many different protein combinations could be prepared recombinantly that produce chimeric proteins and it was also well established that various cytokines have been conjugated to such things as antibodies, ligands, or hormones, to act as site-specific delivery agents (some of which also display functional activity of the cytotoxin). Potter specifically discloses that the immunogenicity of the *P.haemolytica* leukotoxin (a cytotoxin), and fragments thereof, could be made more immunogenic by linking it to a carrier such as proteins, polysaccharides, inactive virus particles and other large, slowly metabolized molecules (column 13). Bell et al. specifically disclose that cytotoxins and cytokines may be linked together to treat disease. It would have been obvious to one of ordinary skill in the art at the time the invention was made that gamma-interferon as disclosed by Bell et al. could be linked to at least one epitope of a leukotoxin derived from *P.haemolytica,* as taught by Potter, because the leukotoxin is a cytotoxin which Bell specifically teaches may be linked to cytokines, such as gamma-interferon, for a dual immune modulating effect. One of ordinary skill in the art would expect to increase the immune response

to the leukotoxin and produce a more efficient vaccine against respiratory disease in ruminants by linking to an immune modulator such as gamma-interferon. Potter specifically discloses that truncated leukotoxin, LKT 352, which lacks cytotoxic activity could be used as the *P.haemolytica* leukotoxin. Bell discloses the use of adjuvants and carriers and it would have been obvious to one of ordinary skill in the art to link the cytotoxin-gammaIFN to a carrier as the use of linking carriers to chimeric proteins was well known in the art for a means of increasing an immune response to an antigen.

13. Claims 37, 40, 44 and 45 are rejected under 35 U.S.C. § 103 as being unpatentable over any one of Lorberboum-Galski et al, Williams et al, Murphy, or Bell et al ('233 or '711) in view of Highlander et al, Strathdee et al, or Lo et al further in view of Prickett.

Each of the primary references disclose the recombinant production of chimeric proteins (also referred to as hybrid protein, fusion proteins, or conjugates) which comprise a cytokine and various different cytokines. Lorberboum-Galski et al specifically disclose a recombinant chimeric protein between IL-2 and Pseudomonas exotoxin (see pages 1922-24). Further disclosed is that various other toxins have been fused/linked to other proteins. The chimeric protein of Williams et al comprises IL-2 and diphtheria toxin (see pages 493-495). Murphy specifically teaches that hybrid proteins can be prepared comprising various cell specific polypeptide ligands, particularly those that contain binding domains for receptor recognition which are conjugated to diphtheria toxin. Il-2 as well as other cytokines are disclosed (col. 3-4). The '233 patent, Bell et al, specifically claims fusion of Beta IFN-gamma IFN; whereas the '711 Bell et al patent specifically

claims gammaIFN-Lymphotoxin. None of these primary references discloses a chimeric protein wherein leukotoxin is the specific cytotoxin for the other fusion partner in the chimeric construct.

Each of the secondary references disclose the cloning of the gene for the leukotoxin from *P.haemolytica* and the DNA/amino acid sequences. Neither of these references teaches the fusion of the leukotoxin to other structural protein. Prickett disclose immunogenic conjugates comprising small peptide regions of leukotoxins and pharmaceutically acceptable carriers or diluents and/or an adjuvant for the use of inducing an immune response against bovine diseases; specifically against shipping fever (see entire patent).

No one prior art reference individually discloses each aspect of the inventive concept; however at the time the invention was made it would have been prima facie obvious and one would have been motivated to substitute the amino acid sequence for the leukotoxin of any one of the secondary references in place of the sequence of the other cytotoxins in the chimeric protein of any one of the primary references in order to obtain a chimeric protein comprising IL-2 or gamma IFN (selected antigens) with leukotoxin for the ultimate use in treating shipping fever. It would have been further obvious to use only short immunogenic/antigenic regions of the leukotoxin instead of the full length cytotoxin, because Prickett had specifically taught that certain immunogenic peptides from leukotoxin could induce an immune response for effective treatment of bovine diseases. In view of the fact that at the time the invention was made it was well known that many different protein combinations could be prepared recombinantly that produce chimeric protein and because it has also been well established that various cytotoxins have been conjugated

to such things as antibodies, ligands, or hormones, to act as site-specific delivery agents (some of which also display functional activity of the cytotoxin), one desirous of treating shipping fever would have found it obvious to use the techniques of the primary reference and construct a chimeric protein comprising IL-2 and/or IFN and the leukotoxin of the secondary reference with the expectation of obtaining a chimeric protein that would be useful to treat shipping fever or other animal infections. One would be further motivated to use IL-2 because it has been shown to be effective against shipping fever. The selection of the appropriate epitopic sequence on the leukotoxin is obvious from the teaching of Prickett in which immunogenic/antigenic peptide regions on the leukotoxin have been identified and used in a manner as disclosed.

Response to Applicant's Arguments:

Applicants argue that the references pertain to attachment of a cytokine to a cytotoxin; however the claims specifically exclude cytokines. This has been carefully considered but is not deemed persuasive. Applicants arguments are not commensurate in scope with the claimed invention. The instant claims, as currently written, read on any antigen and do not exclude cytokines. Applicants should amend the claims to exclude cytokines.

In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1641 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM. *Please note that the name of the Examiner of record has changed from Jennifer Shaver to Jennifer Graser.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027..